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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/687,401 | 10/13/2000 | Ian David Manger | 20174-002300US | 9512 |

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

| EXAMINER | |
|---|---|
| SODERQUIST, ARLEN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1743 | 7 |

DATE MAILED: 09/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/687,401 | Applicant(s) Manger et al. |
|---|---|---|
| | Examiner Arlen Soderquist | Art Unit 1743 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) 1-59 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-59 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5-6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 3-4 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Jo (1999). In the paper Jo teaches fabrication of three-dimensional microfluidic systems by stacking molded polydimethylsiloxane (PDMS) layers. A new technique to fabricate 3D microchannels using polydimethylsiloxane (PDMS) elastomer material is presented. The process allows for the stacking of many thin (about 100 $\mu$m thick) patterned PDMS layers to realize complex 3D channel paths. Replica molding method is utilized to generate each layer. The master for each layer is formed on a silicon wafer using SU-8 positive relief photoresist. PDMS is cast against the master producing molded layers containing channels and openings. To realize thin layers with openings, a sandwich molding configuration was developed that allows precise control of the PDMS thickness. The master wafer is clamped within a sandwich that includes flat aluminum plates, a flexible polyester film layer, a rigid Pyrex wafer and a rubber sheet. A parametric study is performed on PDMS surface activation in a reactive ion etching (RIE) system and the subsequent methanol treatment for bonding and aligning very thin individual components to a substrate. Low RF power and short treatment times are better than high RF power and long treatment times respectively for instant bonding. Layer to layer alignment of less than 15 $\mu$m is achieved with manual alignment techniques that utilize surface tension driven self alignment methods. A coring procedure is used to realize off chip fluidic connections (means for providing a sample fluid to another device) via the bottom PDMS layer, allowing the top layer to remain smooth and flat for complete optical access. Page 225 in the last two sentences teaches the reliable sealing provided by the coring method. After fabricating 3D channel paths, the hydrophobic surfaces of the inside channel walls can be activated (hydrophobic to hydrophilic) an

oxygen plasma RIE system. Page 222 in the introduction teaches many advantages for the use of PDMS in microfluidic devices. The sentence bridging pages 222-223 teach the ability to fabricate various kinds of 3D microfluidic systems including micro-mixers, micro-valves, capillary electrophoresis systems and micro total analysis systems.

3. Claims 1-3, 5-10, 18-24, 31 and 35-44 are rejected under 35 U.S.C. 102(a) as being anticipated by Chan. In the paper Chan teaches microfabricated polymer devices for automated sample delivery of peptides for analysis by electrospray ionization tandem mass spectrometry. Delivery of proteins and peptides to electrospray ionization mass spectrometers (ESI-MS) has been demonstrated using glass and quartz microfabricated devices. This paper reports the construction and use of poly(dimethylsiloxane) (PDMS) microfabricated soft polymer devices with mass spectrometry for protein analysis. The PDMS devices were fabricated using replica molding against a patterned photoresist generated by photolithography techniques. The PDMS devices were connected to the mass spectrometer via a derivatized transfer capillary and samples were transferred by electro-osmotic pumping. The formulation of PDMS was optimized for compatibility with ESI, and the devices were tested for performance. The practical application of PDMS devices was demonstrated by the identification of rat serum albumin separated by 2-D gel electrophoresis. Extended contact of the sample with the surface of the PDMS device did not significantly affect the sample analysis, and the limit of detection for samples run on a PDMS device was comparable to the limit of detection achieved on glass devices. This study suggests that PDMS devices fabricated using replica molding are compatible with ESI-MS. This will potentially lead to the construction of inexpensive microfabricated devices with complex designs and advanced functionalities. The channel has a width of 75 $\mu$m (page 4438).

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 2, 5-30 and 32-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jo as applied to claims 1, 3-4 and 31 above, and further in view of Unger or Duffy and Chan, Figeys (either 1998 Analytical Chemistry article), Parce (US 5,885,470), Ullman or Xue. Jo teaches that many different complex structures can be created bu does not teach specifics of how they can be created or what the will include.

In the paper Unger teaches fabricating valves and pumps for microfluidic devices made of elastomeric materials. The primary material discussed is polydimethylsiloxane for producing the devices and structures. Figure 1 shows the manufacturing process including making two layers having different ratios of monomers in order to bond the layers together. Figure 2 shows different valve and pump configurations made. Figure 4 shows how the peristaltic pump works. The figures also give dimensions that are within the claimed ranges.

In the paper Duffy teaches the preparation of microfluidic systems in polydimethylsiloxane. This paper describes a procedure that makes it possible to design and fabricate (including sealing) microfluidic systems in an elastomeric material-poly(dimethylsiloxane) (PDMS)-in less than 24 hours. A network of microfluidic channels (with width >20 $\mu$m) is designed in a CAD program. This design is converted into a transparency by a high-resolution printer; this transparency is used as a mask in photolithography to create a master in positive relief photoresist. PDMS cast against the master yields a polymeric replica containing a network of channels. The surface of this replica, and that of a flat slab of PDMS, are oxidized in an oxygen plasma. These oxidized surfaces seal tightly and irreversibly when brought into conformal contact. Oxidized PDMS also seals irreversibly to other materials used in microfluidic

systems, such as glass, silicon, silicon oxide, and oxidized polystyrene; a number of substrates for devices are, therefore, practical options. Oxidation of the PDMS has the additional advantage that it yields channels whose walls are negatively charged when in contact with neutral and basic aqueous solutions; these channels support electroosmotic pumping and can be filled easily with liquids with high surface energies (such as water). The performance of microfluidic systems prepared using this rapid prototyping technique has been evaluated by fabricating a miniaturized capillary electrophoresis system. Amino acids, charge ladders of positive and negative charged proteins, and DNA fragments were separated in aqueous solutions with this system with resolution comparable to that obtained using fused silica capillaries.

In the paper Chan teaches microfabricated polymer devices for automated sample delivery of peptides for analysis by electrospray ionization tandem mass spectrometry. Delivery of proteins and peptides to electrospray ionization mass spectrometers (ESI-MS) has been demonstrated using glass and quartz microfabricated devices. This paper reports the construction and use of poly(dimethyl-siloxane) (PDMS) microfabricated soft polymer devices with mass spectrometry for protein analysis. The PDMS devices were fabricated using replica molding against a patterned photoresist generated by photolithography techniques. The PDMS devices were connected to the mass spectrometer via a derivatized transfer capillary and samples were transferred by electro-osmotic pumping. The formulation of PDMS was optimized for compatibility with ESI, and the devices were tested for performance. The practical application of PDMS devices was demonstrated by the identification of rat serum albumin separated by 2-D gel electrophoresis. Extended contact of the sample with the surface of the PDMS device did not significantly affect the sample analysis, and the limit of detection for samples run on a PDMS device was comparable to the limit of detection achieved on glass devices. This study suggests that PDMS devices fabricated using replica molding are compatible with ESI-MS. This will potentially lead to the construction of inexpensive microfabricated devices with complex designs and advanced functionalities. The channel has a width of 75 $\mu$m (page 4438).

In the two sequential 1998 Analytical Chemistry articles Figeys teaches integrated microfluidic devices for protein analysis and identification in which the microfluidic device is connected to an electrospray ionization mass spectrometer.

In the patent Parce teaches controlled fluid transport in microfabricated polymeric substrates. Microfluidic devices are provided for the performance of chemical and biochemical analyses, syntheses and detection. The devices of the invention combine precise fluidic control systems with microfabricated polymeric substrates to provide accurate, low cost miniaturized analytical devices that have broad applications in the fields of chemistry, biochemistry, biotechnology, molecular biology and numerous other fields. Column 5 lines 52-67 teach various polymeric materials including PDMS. Column 12 line 65 to column 13 line 30 teaches the variety of uses for the microfluidic devices including immunoassays.

In the patent Ullman teaches capillary assays involving the separation of free and bound species. The invention concerns methods for masking inhomogeneity of a member of a specific binding pair (sbp) employed in a capillary electroseparation. The method comprises binding the sbp member to synthetic particles that become localized during capillary electroseparation. Also disclosed is one embodiment of the present invention, which is a method for conducting a capillary electroseparation specific binding assay. The method involves the electroseparation of a labeled first member of a specific binding pair that is bound in a complex from labeled first member that is not bound in the complex. The complex comprises the first member and a second member of a specific binding pair. A combination is provided comprising a sample suspected of containing an analyte, a labeled first member of a specific binding pair, and a second member of a specific binding pair under conditions for forming a complex between labeled first member and the second member. The second member either initially or subsequent to the formation of the complex being covalently or noncovalently bound to synthetic particles that migrate uniformly during electroseparation. The combination is subjected to electroseparation and a determination is made as to whether the complex is formed. Also disclosed are kits for conducting a capillary electroseparation specific binding assay. Columns 6-11 teach various things that can be used including enzymes and cells.

In the paper Xue teaches an integrated multichannel microchip electrospray ionization mass spectrometry: analysis of peptides from on-chip tryptic digestion of melittin. In continuation of their work to develop an integrated multichannel microchip interface to electrospray mass spectrometry (ESI-MS), the paper demonstrates one of several applications of this approach in monitoring tryptic digestion products. The multichannel microchip allowed integration of sample preparation onto the microchip to facilitate the analytical process.. Melittin was selected as a model oligopeptide because it possesses a cluster of four adjacent basic residues which enable probing the site specificity of trypsin as a function of digest times. Reactions were performed on-chip in different wells for specific time periods and then analyzed by infusion from the microchip by ESI-MS, using leucine-enkephalin as internal standard. The rate of formation and disappearance of the molecular ion and individual fragments was followed for a melittin-to-trypsin concentration ratio of 300:1. The results indicate the potential of integrating enzymic reactions with multichannel microchip ESI-MS for automated optimization of reaction conditions while consuming only small amounts of sample.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the valves, pumps, analytical devices and sample modification means taught by Unger, Duffy, Chan, Figeys, Parce, Ullman or Xue into the Jo device because of their known use and benefits in microfluidic devices for analysis of samples.

6. Claims 4, 11-17, 25-30, 32-34 and 45-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan as applied to claims 1-3, 5-10, 18-24, 31 and 35-44 above, and further in view of Jo, Unger or Duffy and Figeys (either 1998 Analytical Chemistry article), Parce (US 5,885,470), Ullman or Xue as explained above. Chan does nor teach the microfluidic device being made of two layers of elastomeric material or additional features that might be incorporated into the device. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare modify the Chan device by making the microfluidic device of PDMS as taught by Jo or Unger and include the various features of valves, pumps, analytical devices and sample modification means taught by Unger, Duffy, Figeys, Parce, Ullman or Xue because of their known use and benefits in microfluidic devices for analysis of samples.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art is directed to elastomer use in microfluidic devices.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (703) 308-3989. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

For communication by fax to the organization where this application or proceeding is assigned, (703) 305-7719 may be used for official, unofficial or draft papers. When using this number a call to alert the examiner would be appreciated. Numbers for faxing official papers are 703-872-9310 (before finals), 703-872-9311 (after-final), 703-305-7718, 703-305-5408 and 703-305-5433. The above fax numbers will generally allow the papers to be forwarded to the examiner in a timely manner.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Arlen Soderquist

September 25, 2002

ARLEN SODERQUIST
PRIMARY EXAMINER